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Regioselective intramolecular N_1–C_3 cyclizations on pyrrole–proline to ABC tricycles of dibromophakellin and ugibohlin

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Abstract—Pyrrole N1–C and C3–C regioselective linkage to the fused tricycle ABC system present in the marine metabolites ugibohlin and dibromoisophakellin is described. The cyclization is closely dependent on the electrophilic function, bromination degree of the pyrrole moiety and pH conditions. The mechanism of the functionalization of the ABC olefin by oxidative agents was found to occur through an *N*-acyliminium intermediate as showed by the natural chemical connection between ugibohlin and dibromoisophakellin.

1. Introduction

Marine pyrrole-2-aminoimidazole secondary metabolites, exemplified by dibromophakellin **1**,[1] ugibohlin **2**,[2] dibromoisophakellin **3a** and monobromoisophakellin **3b**,[3] (Fig. 1) have attracted the attention of synthetic organic chemists[4] as a result of their challenging structures and potent biological activities.

More than 70 derivatives have been extracted from different species of marine sponges belonging to the orders Agelasida, Axinellida and Halichondrida. It is currently admitted that these alkaloids are taxonspecific of at least Agelasida order and play the role of chemical markers of these phylogenetically related sponges.[5] Pyrrole-2-aminoimidazole metabolites seem to share a common biogenetic chemical pathway and are probably derived from proline and ornithine.[6]

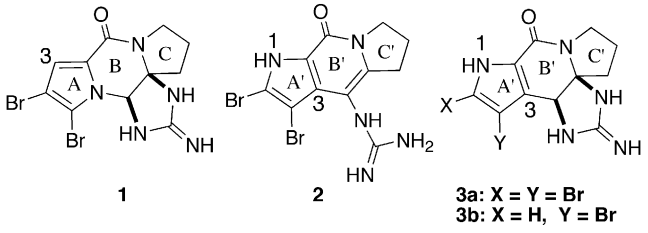

Figure 1. Structures of the marine metabolites containing the N1–C or C3–C tricyclic ABC or A′B′C′ moieties.

In the context of the synthesis of pyrrole 2-aminoimidazole natural alkaloids and their bioactive derivatives, we are interested in pyrrole N1/C3 nucleophilicity permitting a number of strategic connections as in natural compounds **1**–**3**. These compounds are characterized by the presence of the common tricyclic ABC or A′B′C′ moieties (Fig. 1). The selective pyrrole N1–C or C3–C cyclizations seem to be an important step in the formation of a number of natural metabolites belonging to the pyrrole-2-aminoimidazole family. Interesting synthetic approaches studying the stereoselective access to ABC tricycle of dibromophakellin have been recently described.[7]

In our earlier communication on the strategy for building the bicyclic core of longamide,[8] we have outlined the importance of the pyrrolic N1–C and C3–C intramolecular cyclization. Further investigations of the 2-pyrrolecarboxamideacetals reactivity appeared in the literature.[9] The reactivity of the common pyrrole–proline equivalents **4**–**6** (Scheme 1), their regioselective

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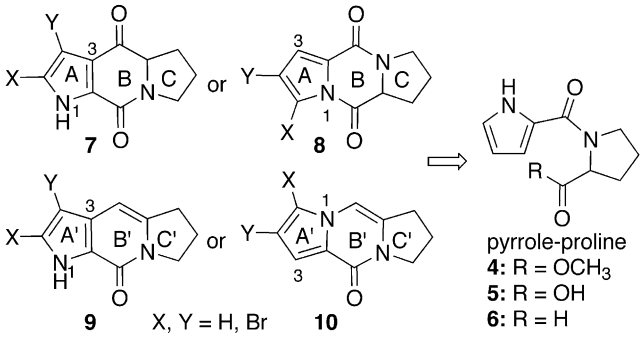


Scheme 1. Targeted ABC and A′B′C′ regioisomers from the pseudo-peptides **4**–**6**.

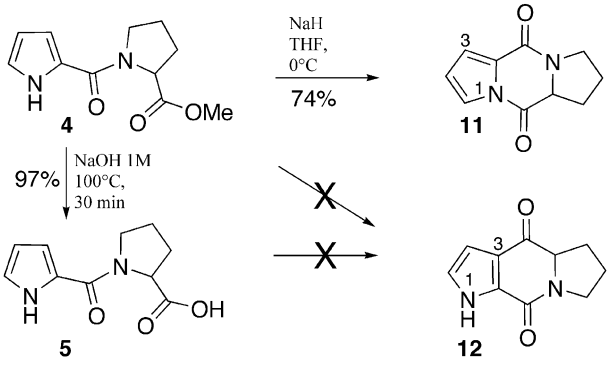
cyclization to the desired regioisomers **7** and **9** or **8** and **10**, the influence of the bromine substitutions on the cyclization became the focus in our studies.

In this letter we report the clear acid/base-mediated N1/C3 regioselective cyclization to ABC or A′B′C′ systems. The functionalization towards the synthesis of ugibohlin and the participation of the determinant *N*-acyliminium in the reactivity of the enamides **9** (Scheme 1) are also discussed.

2. Results and discussion

We started our investigation with the preparation of the pyrrole–proline **4**.[6b] In this case, the commonly used synthesis of amides from primary amines and the 2-(trichloroacetyl)pyrrole in CH_2Cl_2, DMF or acetonitrile did not produce the expected amide. Sterically hindered secondary amide **4** (Scheme 2) was obtained upon EDCI condensation of the pyrrole-2-carboxylic acid and L-proline methyl ester with catalytic amount of DMAP in good yield.

For a close examination of the N1–C and C3–C regioselectivity, several trials have been carried out in different conditions. The subsequent N1–C cyclization of the ester **4**[6b] to pyrazine-1,4-dione derivative **11** was performed most cleanly in THF in presence of NaH (Scheme 2). The unsymmetrical compound **11** is very sensitive to nucleophilic agents. In presence of methanol, **11** gave the ester **4** immediately back.

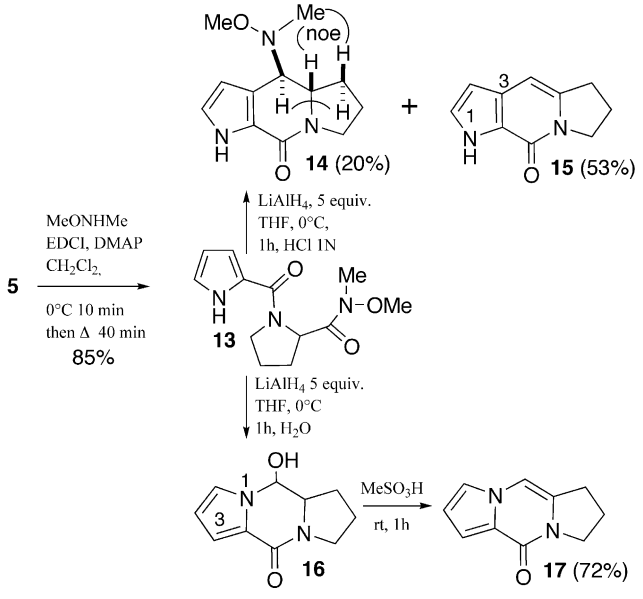


Scheme 2. Direct pyrrole N1–C cyclization.

Further investigation showed that when **4** or **5** were treated under standard conditions like polyphosphoric acid, or methansulfonic acid, C3–C six-membered ring isomer **12** was not detected at all. Internal Friedel–Crafts acylation via the acyl chloride of **5** in presence of Lewis acids did not produce the desired fused 5/6 rings **12**. The size of the cycle and the terminal function of the side chain seem to play together a determinant role in the ring closure. To our knowledge, only one example of such cyclization using flash vacuum pyrolysis at 950 °C was described in the literature.[10] The reaction of sodium methylate with **11** in refluxing methanol produced the methyl ester **4** but not the desired tricyclic product **12**. This result is contrasting with the synthesis of the previously described homologous pyrroloazepine seven members systems.[11] It is interesting to note the similarity of our results with those obtained in indole derivatives[12] revising Röder's results.[13] Therefore we decided to reduce ester **4** into the corresponding aldehyde **6** and to investigate its intramolecular cyclization.

After some exploratory attempts including reduction of **4** with DIBAH reagent, reduction of acid **5** was accomplished through Weinreb intermediate **13** using $LiAlH_4$ at 0 °C. Importantly, the reaction led to the pH dependent C–C compounds **14**[14] and**15** by 1 M HCl treatment and to C–N carbinolamine **16**, which gave **17** in 72% yield after treatment with methansulfonic acid (Scheme 3). N1–C regioisomer **16** was also obtained by Lindel and co-workers.[7a]

Believing that compound **15** could be derived from **14** or vice versa, we have made two complementary experiments from the pure **14** and **15**. Treatment of the unexpected compound **14** in acidic media did not give the elimination compound **15** nor did addition of *N*,*O*-dimethylhydroxylamine to **15** in acidic conditions give the addition compound **14**. Thus, the formation of **14** when



Scheme 3. Cyclization after reduction through Weinreb intermediate. NOE's of **14** are indicated.

the reaction mixture was treated with HCl 1 M indicates the Weinreb-complex participation in the mechanism of the cyclization. Compound **14** was probably formed from the corresponding aldehyde after a complete reduction and hydrolysis of the Weinreb complex.

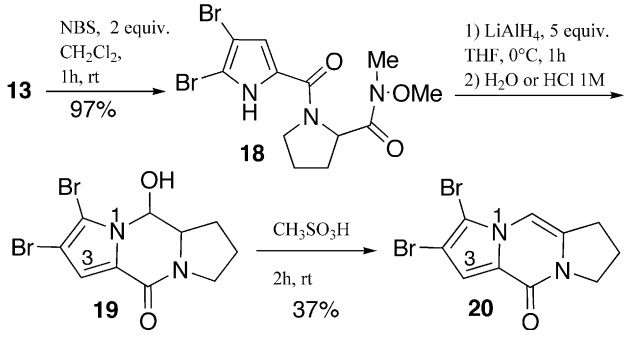
Reduction/cyclization of the brominated intermediate **18** was also investigated to determine if bromine affects the regioselectivity. Compound **18** was prepared directly from **13** in presence of 2 equiv of NBS in 97% yield (Scheme 4). In contrast with the above results, reduction and hydrolysis with both of water or aqueous 1 M HCl gave exclusively the N1–C cyclized carbinolamine **19**. Dehydration of **19** using methansulfonic acid gave **20** in 37% non-optimized yield from **18**.

Apparently, the acid mediated regioselective cyclization is totally masked by the bromine electronic effect. It is clear that in this case, steric effect does not influence the orientation of the cyclization.

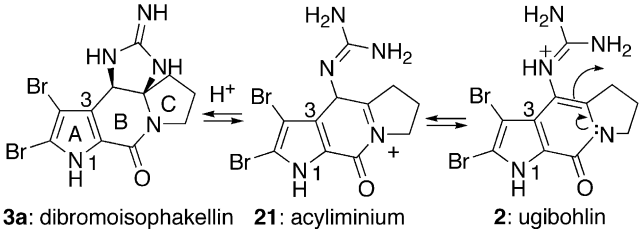
After these results, we decided to study the functionalization of the olefin of the already cyclized non-brominated **15** and to investigate the possible participation of an *N*-acyliminium **21** in the transformation of dibromoisophakellin **3a** into ugibohlin **2** (Scheme 5).

At first test, bromination of **15** with 1 equiv of Br_2 gave a mixture of mono- and di-brominated compounds. Use of 2 or 3 equiv or excess of bromine in acetic acid gave the dibrominated compound **24** in 80% yield (Scheme 6). The tribrominated compound **25** was obtained in 60% yield from **24** with excess of bromine in DMSO.

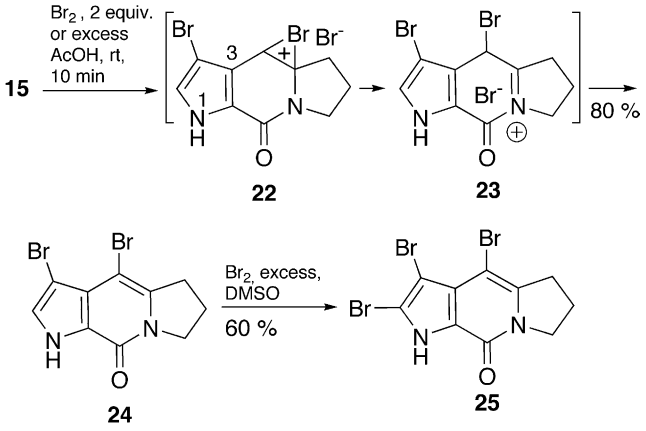
It is also noteworthy that the reaction of **15** with mCPBA gave rise to the formation of the stable quaternary α-hydroxyketone **30** through a twofold epoxidation (Scheme 7). Again, the mechanism of the reaction suggests a participation of the *N*-acyliminium intermediate **27**.



Scheme 4. Selective cyclization after pyrrole bromination.



Scheme 5. Important *N*-acyliminium mechanism connecting the natural dibromoisophakellin and ugibohlin.

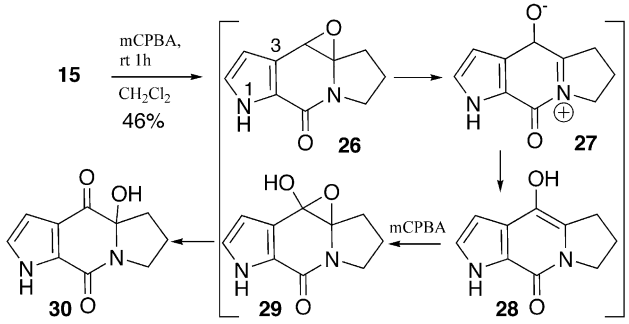


Scheme 6. Bromination and *N*-acyliminium mechanism.

The electron-rich enol **28** is much more reactive than the olefin **15**. Thus treatment with mCPBA (1 equiv or excess) gave the same compound **30** (46%) along with the starting material. We were not able to isolate any intermediate **26**–**29**. The observed over oxidation is facilitated by the rapid rearrangement of **26** into **28** through the *N*-acyliminium **27**. To our knowledge, the pyrrolic C3–C six-membered ring ketone of type **30** is described here for the first time.

Compounds **15**, **24**, **25** and **30** could be further functionalized by metal-catalyzed reactions yielding C–N or C–C cross-coupled derivatives.

We were pleased to find that oxidation with bromine or mCPBA occurs through the valuable *N*-acyliminium but preliminary attempts to introduce the guanidine moiety revealed the necessity to investigate the reaction systematically. The mechanism of the bromination (epoxidation) of the olefin **15** seems to involve stepwise the bromonium bridge **22** (epoxide **26**), then the *N*-acyliminium **23** (**27**) and finally the brominated double bound **25** (**28**). Aiming to progress in the synthesis of the natural product ugibohlin **2**, both of these reactions were carried out in the presence of guanidine but did not enable the addition of the guanidine on the olefin. It is clear that



Scheme 7. Twofold epoxidation by mCPBA.

the kinetic opening of the bromonium or the epoxide into the corresponding iminium form will lay a serious difficulty for the introduction of guanidine. Further work directed to the synthesis of the ugibohlin **2**, dibromoisophakellin **3a** and monobromoisophakellin **3b** using the above studies is currently underway and will be reported soon.

The potent antibiotic, antifungal and anti-inflammatory activities of the most new compounds were evaluated. Only compounds **15** and **20** exhibited a significant antifungal activity towards *Candida tropicalis* (ϕ inhibition of 16 and 27 mm at 100 μg/disk, respectively). In a preliminary assay using a fluorimetric method,[15] compound **24** inhibited both cobra and bee venom phospholipase A_2 with an ID_{50} value of 10 and 2 μg/mL, respectively.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.066. Detailed experimental procedures and characterization for **4–5**, **11**, **13–14**, **17–18**, **20**, **24–25** and **30**.

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